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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,142	02/09/2001	Joan W. Miller	MEE-002	8708

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EXAMINER	
HUYNH, PHUONG N	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 08/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/780,142	MILLER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,8,9,32-35,39-43 and 47-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8,9,32-35,39-43 and 47-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/4/04 has been entered.

2. Claims 1-4, 8-9, 32-35, 39-43 and 47-49 are pending and are being acted upon in this Office Action.

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-4, 8-9, 32-35, 39-43 and 47-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat 6,270,749 B1 (filed June 10, 1999; PTO 892) in view of Adamis et al (Arch Ophthalmol 114(1): 66-71, Jan 1996; PTO 892) or US 6,342,219 B1 (filed April 28, 2000; PTO 892).

The '749 patent teaches a method of treating unwanted choroidal neovasculature such as aged related macular degeneration (See abstract, col. 6, lines 25-42, col. 23, lines 10-11, in particular) comprising endothelial cells in the eyes of a mammal such as New Zealand White

rabbits (see col. 23, line 23, in particular) or subject such as human which is also a primate by administering to the mammal an effective amount of an anti-angiogenic factor such as monoclonal antibody to VEGF (See col. 10, lines 48-50, col. 19, lines 30-45, in particular) conjugated to a tetrapyrrole derivative photosensitizer such as lutetium texaphyrin or LuT2BET, or benzoporphyrin derivatives (See col. 2, lines 65-70, in particular) and irradiating the choroidal neovasculature with laser light (see col. 21, lines 5-8, in particular) such that the light is occlude the choroidal neovasculature (See col. 25, line 31, in particular). The advantage of the reference method is that the PDT treatment is more selective over other technique such as photocoagulation (See col. 25, lines 35-37, in particular).

The invention in claims 1, 33, and 41, differs from the teaching of the reference only in that the method wherein the antibody that binds preferentially to VEGF and is not conjugated to lutetium texaphyrin.

The invention in claim 4, differs from the teaching of the reference only in that the method wherein the anti-angiogenesis factor is administered to the mammal prior to administration of the photosensitizer.

The invention in claim 8, differs from the teaching of the reference only in that the method wherein occlusion of the choroidal neovasculature resulting from the combination of steps (a), (b) and (c) is greater than that resulting from the sum of steps (a), (b) and (c) alone.

The invention in claim 47, differs from the teaching of the reference only in that the method wherein occlusion of the choroidal neovasculature resulting from the combination of steps (a), (b) and (c) is greater than that resulting from the sum of steps (b) and (c) alone.

Adamis et al teach intravitreal injection of neutralizing anti-VEGF antibodies in non-human primate inhibits iris neovascularization (See abstract, in particular).

The '219 patent teaches a method of inhibiting unwanted choroidal neovasculature such as aged related macular degeneration or retinal neovascularization (see col. 21, lines 20-21, col. 22, lines 9-10, col. 102, 64, in particular) by administering unconjugated anti-VEGF antibody such as monoclonal antibody 2C3 simultaneously with, before, or after surgery or radiation treatment; or are administered to patients with, before, or after conventional chemotherapeutic, radiotherapeutic or anti-angiogenic agents such as angiostatin (See col. 120, line 59, Table D, in particular), or targeted immunotoxins or coaguligands (See col. 123, lines 9-10, Paragraph 461, in particular). The '219 patent teaches the advantage of anti-VEGF antibodies is that it inhibit

VEGF binding to the VEGFR2 whereas other anti-VEGF antibody binds to VEGFR1 (See col. 3, line 16, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to administer to a mammal an unconjugated lutetium texaphyrin for a method of unwanted choroidal neovasculature in a mammal as taught by the '749 patent in combination with the anti-VEGF as taught by Adamis et al or the'219 patent or the angiostatin as taught by the '219 patent before administering photosensitizer as taught by the '219. It has been well established in the art that anti-VEGF conjugated lutetium texaphyrin is from unconjugated anti-VEGF and lutetium texaphyrin and there is no evidence that the method of use described in the instant claims would differ in an unexpected manner from those described in the reference. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with an expectation of success to do this because the '749 patent teaches tetrapyrrole derivative photosensitizer such as lutetium texaphyrin or LuT2BET, or benzoporphyrin derivatives is effective for treating unwanted neovascularization and PDT treatment is more selective over other technique such as photocoagulation (See col. 25, lines 35-37, in particular). Adamis et al teach intravitreal injection of neutralizing anti-VEGF antibodies in non-human primate inhibits iris neovascularization (See abstract, in particular). The '219 patent teaches anti-VEGF antibody in combination with other therapeutic agent is effective for inhibiting unwanted choroidal neovasculature such as aged related macular degeneration or retinal neovascularization (see col. 21, lines 20-21, col. 22, lines 9-10, col. 102, 64, in particular) and angiostatin inhibits angiogenesis (See col. 120, line 59, Table D, in particular). The '219 patent further teaches that the advantage of anti-VEGF antibodies is that it inhibit VEGF binding to the VEGFR2 whereas other anti-VEGF antibody binds to VEGFR1 (See col. 3, line 16, in particular). Adamis et al teach intravitreal injection of neutralizing anti-VEGF antibodies in non-human primate inhibits iris neovascularization (See abstract, in particular). Given the lack of objective evidence that the method of use described in the instant claims for treating the same population having the same disease would differ in an unexpected manner from those described in the reference, one would expect that the occlusion of the choroidal neovasculature resulting from the combination of steps (a), (b) and (c) is greater than that resulting from the sum of either steps (a), (b) and (c) alone.

6. Claims 1-4, 8-9, 32-35, 39-43 and 47-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kramer *et al* (Ophthalmology 103(3): 427-38, March 1996; PTO 892) in view of Adamis et al (Arch Ophthalmol 114(1): 66-71, Jan 1996; PTO 892) or US 6,342,219 B1 (filed April 28, 2000; PTO 892).

Kramer *et al* teach a method of treating unwanted choroidal neovasculature (CNV) by administering to a mammal such as cynomolgus monkeys a benzoporphyrin derivative verteporfin liposome, and then irradiating the choroidal neovasculature with laser light to occlude the choroidal neovasculature (See abstract, in particular). The reference method is effective for treatment of choroidal neovascularization with minimal retinal and choroidal damage and no major local adverse effects (See abstract, in particular).

The invention in claims 1, 33, and 41, differs from the teaching of the reference only in that the method wherein the antibody that binds preferentially to VEGF is administered prior to administering the photosensitizer.

The invention in claim 4, differs from the teaching of the reference only in that the method wherein the anti-angiogenesis factor is administered to the mammal prior to administration of the photosensitizer.

The invention in claim 8, differs from the teaching of the reference only in that the method wherein occlusion of the choroidal neovasculature resulting from the combination of steps (a), (b) and (c) is greater than that resulting from the sum of steps (a), (b) and (c) alone.

The invention in claim 47, differs from the teaching of the reference only in that the method wherein occlusion of the choroidal neovasculature resulting from the combination of steps (a), (b) and (c) is greater than that resulting from the sum of steps (b) and (c) alone.

Adamis et al teach intravitreal injection of neutralizing anti-VEGF antibodies in non-human primate inhibits iris neovascularization (See abstract, in particular).

The '219 patent teaches a method of inhibiting unwanted choroidal neovasculature such as aged related macular degeneration or retinal neovascularization (see col. 21, lines 20-21, col. 22, lines 9-10, col. 102, 64, in particular) by administering unconjugated anti-VEGF antibody such as monoclonal antibody 2C3 simultaneously with, before, or after surgery or radiation treatment; or are administered to patients with, before, or after conventional chemotherapeutic, radiotherapeutic or anti-angiogenic agents such as angiostatin (See col. 120, line 59, Table D, in particular), or targeted immunotoxins or coaguligands (See col. 123, lines 9-10, Paragraph 461, in particular). The '219 patent teaches that the advantage of anti-VEGF antibodies is that it inhibit

VEGF binding to the VEGFR2 whereas other anti-VEGF antibody binds to VEGFR1 (See col. 3, line 16, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine anti-angiogenesis factor as taught by Adamis et al and the '219 patent by administering the antibody that binds specifically to VEGF as taught by Adamis et al and the'219 patent before administering the benzoporphyrin derivative verteporfin liposome for a method of treating unwanted choroidal neovasculature as taught by Kramer *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with an expectation of success to do this because the Kramer *et al* teach benzoporphyrin derivative verteporfin liposome is effective for treatment of choroidal neovascularization with minimal retinal and choroidal damage and no major local adverse effects (See abstract, in particular). Adamis et al teach intravitreal injection of neutralizing anti-VEGF antibodies in non-human primate inhibits iris neovascularization (See abstract, in particular). The '219 patent teaches the anti-VEGF antibody can be administered to patient before conventional chemotherapeutic treatment and the advantage of anti-VEGF antibodies is that it inhibit VEGF binding to the VEGFR and is effective as a method of inhibiting unwanted choroidal neovasculature such as aged related macular degeneration or retinal neovascularization (see col. 21, lines 20-21, col. 22, lines 9-10, col. 102, 64, in particular). Given the lack of objective evidence that the method of use described in the instant claims for treating the same population having the same disease would differ in an unexpected manner from those described in the reference, one would expect that the occlusion of the choroidal neovasculature resulting from the combination of steps (a), (b) and (c) is greater than that resulting from the sum of either steps (a), (b) and (c) alone.

7. Claims 1-4, 8-9, 32-35, 39-43 and 47-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kramer *et al* (Ophthalmology 103(3): 427-38, March 1996; PTO 892) in view of Adamis *et al* (Arch Ophthalmol 114(1): 66-71, Jan 1996; PTO 892) or US 6,342,219 B1 (filed April 28, 2000; PTO 892) as applied to claims 1-4, 8-9, 33-35, 39-43 and 47-49 mentioned above and further in view of US Pat No 5,733,876 (March 1998, PTO 892).

The combined teachings of Kramer *et al,* Adamis *et al* and the '219 patent have been discussed supra.

The claimed invention differs from the combined teachings of the references only in that the anti-angiogenic factor is angiostatin.

The '876 patent teaches a method of inhibiting angiogenesis or growth of endothelial cells associated with macular degeneration (see column 9, line 66 bridging column 10, line 9-10, in particular) by administering an anti-angiogenic factor such as angiostatin (See claims 1-13 of '876, abstract, in particular). The reference angiostatin may be used in combination with other compositions and procedures for the treatment of any diseases associated with endothelial cell proliferation (See column 10, line 20-21, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the anti-VEGF antibody for a method of treating unwanted choroidal neovasculature as taught by Adamis *et al* and the '219 patent for the angiopoietin as taught by the '876 patent by administering the angiopoietin before any conventional therapy as taught by the '219 patent, follows by administering the benzoporphyrin derivative verteporfin liposome that is effective for treatment of choroidal neovascularization as taught by Kramer *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated with an expectation of success to do this because the Kramer *et al* teach benzoporphyrin derivative verteporfin liposome is effective for treatment of choroidal neovascularization with minimal retinal and choroidal damage and no major local adverse effects (See abstract, in particular). The '876 patent teaches angiostatin may be used in combination with other compositions and procedures for a method of inhibiting angiogenesis or growth of endothelial cells associated with macular degeneration (see column 9, line 66 bridging column 10, line 9-10, in particular). Given the lack of objective evidence that the method of use described in the instant claims for treating the same population having the same disease would differ in an unexpected manner from those described in the reference, one would expect that the occlusion of the choroidal neovasculature resulting from the combination of steps (a), (b) and (c) is greater than that resulting from the sum of either steps (a), (b) and (c) alone.

8. Claims 1-4, 8-9, 32-35, 39-43 and 47-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kramer *et al* (Ophthalmology 103(3): 427-38, March 1996; PTO 892) in view of Adamis *et al* (Arch Ophthalmol 114(1): 66-71, Jan 1996; PTO 892) or US 6,342,219 B1 (filed April 28, 2000; PTO 892) as applied to claims 1-4, 8-9, 33-35, 39-43 and 47-49 mentioned above and further in view of US Pat No 6,270,749 B1 (of record, Aug 2001, PTO 892).

The combined teachings of Kramer *et al,* Adamis *et al* and the '219 patent have been discussed supra.

The claimed invention differs from the combined teachings of the references only in that the method of treating unwanted choroidal neovasculature wherein the tetrapyrrole derivative is lutetium texaphyrin instead of benoporphyrin derivative Verteporfin.

The '749 patent teaches the use of photosensitizer such as texaphyrin complex with a diamagnetic metal such as Lutetium which is a tetrapyrrode derivative (See Abstract, column 8, lines 5-17, in particular) for a method of treating age-related macular degeneration (See column 23, lines 6-11, in particular). The '749 patent teaches the advantages of Lutetium texaphyrin are: (1) it posses a strong, broad fluorescence emission profile in the near-infrared centered around at 750 nm that is not obstructed by endogenous chromophores, thereby exhibiting significant advantages over conventional fluorescein angiography, (2) Lutetium texaphyrin exhibits rapid plasma clearance in humans thereby minimizing cutaneous phototoxicity compared with other photosensitizers (See column 8, lines 8-16, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the benoporphyrin derivative Verteporfin as a method of treating choroidal neovascularization as taught by Kremer et al for the leutetium texaphyrin as taught by the '749 for a method of treating unwanted choroidal neovasculature in a mammal as taught by Kramer *et al,* Adamis *et al* the '219 patent and the '749 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '749 patent teaches photosensitizer such as Lutetium texaphyrin is effective as a method of treating unwanted choroidal neovasculature associated with age-related macular degeneration because the advantages of Lutetium texaphyrin are: (1) it posses a strong, broad fluorescence emission profile in the near-infrared centered around at 750 nm that is not obstructed by endogenous chromophores, thereby exhibiting significant advantages over conventional

fluorescein angiography, (2) Lutetium texaphyrin exhibits rapid plasma clearance in humans thereby minimizing cutaneous phototoxicity compared with other photosensitizers (See column 8, lines 8-16, in particular). Given the lack of objective evidence that the method of use described in the instant claims for treating the same population having the same disease would differ in an unexpected manner from those described in the reference, one would expect that the occlusion of the choroidal neovasculature resulting from the combination of steps (a), (b) and (c) is greater than that resulting from the sum of either steps (a), (b) and (c) alone.

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

11. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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